Antibiotic Use During Cold and Flu Season

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It's that time of year again – cold and flu season! With the increased incidence of upper respiratory tract infections is the growing number of antibiotic prescriptions. Although antibiotic use is warranted in many of these cases, they are also frequently prescribed for viral infections. Many clinical trials have shown that patients receiving antibiotic therapy for acute bronchitis, cough and upper respiratory illnesses have similar outcomes to those patients taking placebo. Despite this evidence, 50-60% of 51 million visits for these infections (usually of viral origin) in the U.S. result in a patient receiving an antibiotic prescription.[1]

One main key in preventing these illnesses is improving the use of influenza and pneumococcal vaccines in all eligible candidates, such as those with chronic pulmonary or cardiovascular diseases. When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70-90% of healthy adults less than 65 years of age.[2] The influenza vaccine is administered annually, while the pneumococcal vaccine is given once, then readministered five years later if appropriate.[3] The ideal time for influenza vaccine administration is October and November, but it is still not too late since cold and flu season does not end until March or early April.[2] An adult immunization schedule can be found at the Centers for Disease Control and Prevention (CDC) website: www.cdc.gov/nip.[3] Because of the unusually high demand for influenza vaccine this season, the CDC is working with various medical groups (e.g., American Medical Association, managed care organizations, etc.) and regional health departments to redistribute vaccine supplies where needed. The local or state health department should be contacted for more information about vaccine availability.

When a patient does develop an infection, it is often difficult to differentiate between a viral and a bacterial infection. An example of this is in patients with rhinosinusitis. Some signs and symptoms that would suggest a bacterial infection include:

- purulent nasal discharge,
- maxillary tooth or facial pain (especially when unilateral),
- unilateral maxillary sinus tenderness,
- worsening symptoms after initial improvement, and
- symptoms lasting greater than seven days.[4]

If an antibiotic is warranted, a narrow-spectrum antibiotic should be considered. Studies have shown that newer and broad-spectrum antibiotics (e.g., quinolones and second generation macrolides) are not significantly more effective than narrow-spectrum agents (e.g., amoxicillin, co-trimoxazole).[4] In order to provide an example of how frequently broad-spectrum antibiotics are prescribed, Table 1 shows the antibiotics within the four main antibiotic classes (i.e., penicillins, macrolides, cephalosporins, and quinolones) most prescribed by Kansas Medical Assistance Program providers from Novermber 2002 through October 2003.

Table 1: Top Drug Prescribed Within Antibiotic Classes

Class	Top Drug	Rx
Penicillins	Amoxicillin	56,846
Macrolides	Azithromycin	42,790
Cephalosporins	Cephalexin	28,013
Quinolones	Levofloxacin	20,858

In comparison to total antibiotic use, amoxicillin was prescribed 24.7% of the time, while azithromycin was prescribed 19.0% of the time. Translated in terms of financial impact, the amount paid by Kansas Medical Assistance Program for amoxicillin was approximately $464,000 (5.2% paid for all antibiotics), while the amount paid for azithromycin was $1,629,000 (18.3% paid for all antibiotics).

Although drug costs should be a concern, the main concern with the prescribing of antibiotics for viral infections and the underutilization of narrow-spectrum antibiotics is *antibiotic resistance*. In an effort to reduce the spread of antibiotic resistance, a panel consisting of representatives from the medical areas of family practice, internal medicine emergency medicine and infectious disease, as well as the Centers for Disease Control and Prevention (CDC), was formed. This group formulated principles for the evaluation and treatment of acute bronchitis, acute sinusitis, pharyngitis and upper respiratory tract infections. With the dissemination of these principles (which can be found in several professional society journals), the panel hopes that providers will be provided with strategies for improved antibiotic prescribing.[5]

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We welcome the opportunity to discuss with you any comments or concerns you may have about this Newsletter.

Heritage Information Systems, Inc.

Kansas Medical Assistance Program

Drug Utilization Review Bulletin

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Highlight on Heart Failure

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Heart failure (HF) affects almost five million Americans and 400,000 to 700,000 new cases are being diagnosed annually. The incidence and prevalence of heart failure continues to rise, despite recent clinical trials showing that certain drugs may reduce the morbidity and mortality associated with heart failure. This trend is expected to continue as the population ages and more patients survive myocardial infarctions.[2]

HF is the most common cause of hospitalizations in patients greater than 65 years old and accounts for approximately 300,000 deaths per year. It also accounts for a large amount of health care expenditures costing approximately $20 to 40 billion each year, which does not include indirect costs due to lost productivity.[1,3] Nearly 70% of the economic burden of HF is due to hospitalization and up to two-thirds of these hospitalizations may be preventable.[1,4-6]

Studies have shown that angiotensin converting enzyme (ACE) inhibitors decrease morbidity and mortality in patients with heart failure. All patients with left-ventricular dysfunction heart failure should be given an ACE inhibitor at a therapeutic dose unless particular contraindications are present.[1,3] See Table 1 for ACE inhibitor dosing. Contraindications for ACE inhibitors include:

- angioedema,
- anuric renal failure and
- pregnancy.

Physicians are often reluctant to use or use subtherapeutic doses of ACE inhibitors because of potential side effects including hypotension, cough or worsening renal function. ACE inhibitors should be used with caution in the following cases:

- very low blood pressure,
- markedly increased serum creatinine (>3.0 mg/dL),
- bilateral renal artery stenosis, and
- elevated potassium levels (>5.5 mmol/L).

Symptomatic hypotension that occurs with initial doses of an ACE inhibitor may not recur with repeated doses. Cough is also a frequent side effect of ACE inhibitors, but because of the long term benefits, patients should be encouraged to continue their use if the cough is not severe.

Unless contraindicated, angiotensin II receptor antagonists (AIIRA) therapy should be considered in HF patients who are intolerant to ACE inhibitors. Valsartan (Diovan®) is currently the only AIIRA with an FDA indication for use in patients with chronic heart failure who are intolerant to the ACE inhibitors. The combination of hydralazine and isosorbide dinitrate may also be an option if ACE inhibitors cannot be tolerated.[1,3]

Beta-blocker use in HF was once thought to be harmful. However, it is now known that the appropriate use of these agents can substantially decrease HF morbidity and mortality.[8-10] Current practice guidelines recommend the use of beta blockers in all patients with stable HF due to left ventricular dysfunction, unless the use of these medications is contraindicated or not tolerated. Contraindications include:

- Hospitalized in an intensive care unit
- Evidence of fluid overload or severe volume depletion
- Recent requirement for intravenous treatment with positive inotropic agent
- Reactive airways disease requiring inhaled ß-adrenergic agonist therapy
- Symptomatic bradycardia or advanced heart block without a pacemaker.

Currently only carvedilol (Coreg®) and metoprolol controlled release (Toprol®) have FDA approval for use in HF. Bisoprolol (Zebeta®) is not yet approved for HF but it has demonstrated efficacy in clinical studies. See table 2 for recommended dosing for patients with HF.

Aldosterone blockade reduces mortality and morbidity among patients with severe HF. Low dose spironolactone (12.5mg to 25mg/day) should be considered in patients with severe HF (class III or IV), who have been maximized on all other recommended therapies (including ACE inhibitors), and have preserved renal function (serum creatinine less than 2.5mg/dl) and normal potassium concentrations (less than 5mmol/L.[3] Eplerenone (Inspra®), a selective aldosterone blocker, has recently received FDA approval for the treatment of HF post myocardial infarction. The recommended dose is 25 mg daily titrated to 50mg daily preferably within four weeks as tolerated by the patient. Eplerenone is contraindicated in patients with a serum potassium > 5.5 mEq/L at initiation, a creatinine clearance ≤ 30 ml/min and concomitant use of potent

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CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir).[7]

The effect of certain medications on HF symptoms, progression, and survival is well known.[4-6] However less is known about the factors leading to hospitalization. Numerous factors that may precipitate HF exacerbation have been implicated and often these factors are considered avoidable. Table 3 provides a list of risk factors associated with heart failure exacerbation.

Earlier recognition of symptoms of heart failure exacerbation, improved medication use, and more timely intervention are ways to improve care. Improving the HF patient's understanding of their disease and self-management is key in improving HF outcomes. Patient education should include instruction on compliance with drug regimens, compliance with a low sodium diet to avoid fluid retention, recognition of symptoms and actions to take when symptoms appear, and contacting their healthcare professional when questions and concerns arise[11].

Table 1. Angiotensin Converting Enzyme (ACE) Inhibitor Dosing

Drug Name	Target HF Dose Total mg per day*	Administration Regimen
Benazepril (Lotensin)	20 – 40	QD or Divided BID
Captopril (Capoten)	150	Divided TID
Enalapril (Vasotec)	20- 40	Divided BID
Fosinopril (Monopril)	20 – 40	QD
Lisinopril (Zestril, Prinivil)	20 - 40	QD
Moexipril (Univasc)	15 – 30	QD or Divided BID
Perindopril (Aceon)	4 – 8	QD or Divided BID
Quinapril (Accupril)	20 – 40	Divided BID
Ramipril (Altace)	10	Divided BID
Trandolapril (Mavik)	4	QD or Divided BID

* FDA-labeled regimens. Target doses for HF are associated with morbidity and/or mortality benefits in randomized controlled trials. Titrate slowly over a 2-week period from individually recommended starting doses for each product to the recommended target dose. Lower doses should be utilized if target doses are not tolerated.
Dosing on benazepril, moexipril, perindopril reflect usual dosage range for hypertension (target HF doses on these products are not available).

Table 2. Recommended Doses of ß-Blocker for Patients with Chronic Heart Failure [12,13]

ß-Blocker	Initial Total Daily Dose (mg)*	Maximum Total Daily Dose (mg)	Administration Regimen
Bisoprolol fumarate (Zebeta®, generic)	1.25	10	Once daily
Carvedilol (Coreg®)	6.25	50/100†	Divided twice daily
Metoprolol Succinate, extended release (Toprol XL®)	12.5/25‡	200	Once daily

* Prior to initiation of therapy, minimize fluid retention and stabilize dosing of ACE inhibitors and digoxin, if used. Dosage should be individualized and closely monitored during titration. Initial doses should be taken for 2 weeks. If tolerated, double the dose at least every 2 weeks to the highest tolerated dose, not to exceed the recommended maximum daily dose.
†Dose of 25 mg twice daily for body weight < 85 kg and 50 mg twice daily for body weight ≥ 85 kg
‡ Dose of 25 mg recommended for NYHA Class II patients and 12.5 mg for NYHA Class III-IV patients.

Table 3. Potential Precipitants of Heart Failure Exacerbations[3-4, 11,14-21]

Medication Related	Comorbidities	Other

• Noncompliance with medications
• Use of inappropriate medications:
  • Antiarrhythmic agents (except amiodarone)
  • Calcium channel blockers (except amlodipine or felodipine)
• NSAID use
• Use of thiazolinediones (I.e., pioglitazone, rosiglitazone
• Underutilization or sub-optimal doses of ACE inhibitors
• Underutilization of beta blockers
• Inappropriate reductions in HF medications
	• Uncontrolled hypertension
	• Depression
	• Myocardial ischemia
	• Arrhythmias (primarily tachyarrhythmias)
	• Cardiomyopathy
	• Miscellaneous non-cardiac disorders (e.g., pulmonary infectious processes)
	• Renal Insufficiency
	• Anemia
		• New York Heart Association classification III to IV
		• Advanced age
		• Excessive salt intake (greater than 2000-3000mg per day)
		• Noncompliance with diet

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Clinical Analysis on Heart Failure

As announced in the October newsletter, Heritage Information Systems, Inc. (Heritage) was selected to provide Clinical Management Services for the Kansas Medical Assistance Program. The Clinical Management division specializes in prior authorization and prospective drug utilization review (ProDUR) editing programs, retrospective drug usage evaluation (DUE) development and implementation of disease management programs, pharmacoeconomic and outcomes analyses, and pharmacy program consulting services. Recently, Heritage performed a clinical analysis on patients with a diagnosis of heart failure (HF). The following table highlights three heart failure indicators: Underuse of ACE inhibitors, underuse of beta-blockers and increased risk of adverse drug event: use of thiazolidinediones. Underutilization of ACE inhibitors and beta-blockers was identified in 22.2% and 44% of patients with HF, respectively. The use of thiazolinediones was identified in 694 patients with a diagnosis of heart failure.

Selected Heart Failure Indicators

Indicators (by type):	Except ons*:	Cand dates†:	% of Except ons:
Underuse: ACE Inh	2960	13322	22.2%
Underuse: Beta b ocker§	3258	7496	43.5%
Increase r sk of adverse drug event: Use of azolidinediones (i.e., p tazone, ros itazone)			91.2

*Exceptions are those patients with heart failure identified as potential intervention opportunities
†Candidates are t hose patients with a documented or inferred history of heart failure (i.e., underuse of ACE inhibitor), a documented history of heart failure (i.e, underuse of beta blocker) or receiving a thiazolidinedione (i.e., Increased risk of adverse drug event: Use of thiazolidinediones).
‡Using submitted medical claims data, patients with renal failure, angioedema, pregnancy, renal artery stenosis were excluded
§Using submitted medical claims data, patients with asthma, cardiac conduction disorders without pacemaker placement, fluid overload or volume depletion, or patients receiving infusion therapy with sympathomimetics.